Characterization and re-evaluation of experimental pain models in healthy subjects

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Chapter 9

GENERAL DISCUSSION

Pain is a complex, multifactorial symptom that remains poorly understood and an unmet clinical need. Pain is influenced by many factors, like psychological factors, functional activities, genetics, gender, race, emotional functioning, social context, and education level and socioeconomical concerns. Pain is an individualized unpleasant sensory and emotional experience which is associated with actual or potential tissue damage, or described in terms of such damage.[8] The ideal species for the study of pain is the human being, in particular chronic pain patients. However, pain in these patients is almost always influenced by fear, emotion, anxiety, cognitive and autonomic responses, general malaise, etcetera.[3] Various approaches in search of the "magic drug" for pain palliation have arisen, leading to an exponential increase in health care costs.[1,2] This process is complicated by a number of factors: our access to the human organism is limited as ethical restrictions apply to all manipulations involving healthy subjects or patients, a lack of understanding about the underlying pathophysiological mechanisms, and the poor predictive validity of the current models of evoked pain used for the screening of novel compounds.

Healthy subject studies with human evoked pain models are an Alternative to investigate (novel) analgesics. With these pain models researchers can explore different pain mechanisms in a controlled setting. Different modalities of pain (*e.g.*, mechanical, thermal, electrical, or chemical) can be applied to different tissues (*i.e.*, skin, muscles, or viscera) for the assessment of various pain pathways. When intensity, duration, frequency, and localization of the stimulus can be controlled and a stable and reproducible outcome can be measured, a valid pain model is established. This can subsequently be used for the evaluation of analgesic activity and to demonstrate active dose ranges in early clinical phase of drug development. Pain models are able to induce a single or a composition of multiple positive somatosensory symptoms, making them suitable to investigate phenomena like nociceptive and inflammatory pain, and, to a lesser degree, hyperalgesia and allodynia, demonstrating some similarities to mechanisms present in neuropathic pain. These paradigms aim to activate different nociceptors and evoke pain through specific pathways and mechanisms, but difficulties remain in the exact determination of the activated pathways and pain mechanisms.[9] Studies measuring the effect of analgesic compounds on evoked pain make it clear that some drugs can yield significant results in one pain model but can fail to have an analgesic effect when using a different pain model.[10-12] Multimodal testing gives the opportunity to activate multiple receptor types and mechanisms. This multimodal test approach has shown its value in this thesis. For example, the high dose of PF-06372865, a $GABA_A$ positive allosteric modulator, evaluated in **Chapter 2**, increased the PTT to pressure stimulation and the cold pressor test, but not of the CPM or heat stimuli, and in **Chapter 3** a high dose of PF-06273340 (pan-Trk inhibitor) significantly affected the heat pain threshold, but not the cold pressor pain thresholds, or the electrical or pressure pain thresholds. Hence, these combined models may increase the knowledge regarding effects of analgesic compounds on peripheral and central pain mechanisms, and are therefore better suited for pharmacological testing. Combining the testing of various pain mechanisms provides the opportunity to obtain a more complete impression of the analgesic profile of a drug and increase the predictive value of nociceptive testing in healthy subjects for analgesic efficacy in patients with pain. The analgesic profiles of drugs appear to be unique and related to the pharmacology of the drug, in which case they may turn out to be specific for drug class, evidence of which may be seen in **Chapter 2 -4 & 6**.

Comparable to the uniqueness of the profile of analgesics with respect to their effects on a battery of human evoked pain models, patients with chronic pain show selectivity in their response to different analgesics. Particularly in patients with neuropathic pain, a high degree of variability in pain relief is observed, even among patients with identical diagnostic aetiologies, such as diabetic neuropathy or post-herpetic neuropathy. This high interpatient variability has frustrated responses to analgesics, both in clinical practice as in clinical trials.

Historically, neuropathic pain is classified based on aetiology (*e.g.*, nerve lesion, infection or diabetes), Although similar symptoms and signs are frequent across different aetiologies. It is this heterogeneity in pain patients that may have obscured positive results in certain subgroups due to the presence of multiple pain mechanisms within a diagnostic patient population. It has become apparent that this approach to classify pain patient might not be adequate, supported by the obtained results in late stage trials where promising candidate analgesic have failed to produces satisfying pain reductions.[13-15] Better patient stratification might improve clinical trial outcome, for example by classification based on somatosensory phenotypes. This more mechanism of action based approach is justified because variability between different pain syndromes was found to be smaller than between patients.[4,5,16]

Somatosensory phenotypes are patterns of somatosensory abnormalities and their likely underlying mechanisms.[14,16-21] These different phenotypical presentations possibly reflect different dysfunctions in somatosensory processing and defining them might give a better understanding to the underlying mechanisms of pain generation. Quantitative sensory testing (QST) is a comprehensive way of assessing the somatosensory phenotype in patient with pain.[22,23] QST evaluates

somatosensory modalities, such as temperature, touch, vibration, and pain. It provides information on the condition of peripheral sensory nerves, as well as central sensitization and pain perception. QST allows for the evaluation of the functional status of the small (Aδ, C) and large (Aβ) fiber sensor systems.[6,23] It enables one to create a sensory profile of the patient, which in some ways is comparable to the way human evoked pain models aid in the definition of an analgesic profile of a drug.

Before implementation of this new mechanism based approach, the challenge is to characterize the somatosensory phenotypes and the response each phenotype demonstrates on different analgesics. Identification of phenotypic profiles with the most predictive value in analgesic efficacy ideally are then linked to the analgesic profiles created by the PainCart. Subsequently, this process can be reversed: a mechanism of action based approach can be deployed where the predictive value of the PainCart leads to the selection of a cluster(s) of somatosensory phenotypes with a similar mechanistic aetiology, increasing the chance to yield positive outcomes.

This thesis focused on profiling novel and currently existing analgesic compounds using the PainCart. The analgesic profiles are part of the mechanism of action based approach and may serve as a predictive tool to select the correct somatosensory phenotype for further evaluation of a compound. Below a first attempt is made to couple these analgesic profiles to a somatosensory phenotype derived from QST testing.

MAIN OUTCOMES

In **Chapter 2-4** the analgesic potential of novel analgesic compounds was assessed. These three studies were conducted with a single-dose, double-blind, randomized, cross-over design with positive and placebo controls in healthy subjects. The PainCart was used as the multimodal test setting. The results of each study provided a comprehensive analgesic profile of the investigated drug. **Chapter 2** describes the results of two dose levels of PF-06372865, and α2/α3/α5 subtype selective γ-Aminobutyric acid ($GABA_A$) partial agonist. PF-06372865 is a potent ligand of the allosteric benzodiazepine site of the $GABA_A$ receptor, which exhibits functional selectivity for receptors containing α2/α3/α5 over those containing α1, postulating a better analgesic efficacy with fewer sedative side effects. The PainCart showed an increase in the pressure pain tolerance threshold (PTT) in both dose levels and an increase in the cold pressor PTT in the high dose level. Additionally, no sedation or other intolerable adverse events were observed which would limit its clinical use. Despite these promising results, a lack of analgesic efficacy was shown in a study with chronic lower back pain (CLBP) patients.[27] It was hypothesized that a α1-sparing, partial subtype-selective $GABA_A$ positive allosteric modulator would achieve higher receptor occupancy (RO) than a benzodiazepine without limiting adverse events (AEs) and demonstrate analgesia, Although patient benefit derived from benzodiazepines has never been established. Results from Cochrane reviews have highlighted that the evidence base for the treatment of CLBP with benzodiazepines is weak and indicates that there is insufficient evidence to recommend prescribing benzodiazepines for back pain.[37] It could be debated that CLBP patients were chosen erroneously for further exploration of the analgesic effects of PF-06372865. Nmerous high-quality randomized controlled trials have been performed on patients with CLBP and none of them exerted positive results for neuropathic CLBP syndromes.[7,74-78] It would have been worth considering to explore analgesic efficacy of PF-076372865 by linking the analgesic profile created by the PainCart to a surrogate somatosensory phenotype. Baron et al. revealed distinct phenotypes shown through QST profiling of pain patients with different aetiologies.[79] The cluster 2 and 3 phenotypes were most affected by cold and pressure pain thresholds, which were the pain models most affected by PF-06372865. Patients with post-herpetic neuralgia are mostly represented in cluster 2 and 3 (approximately 80%).[79] Perhaps it would have been more beneficial to choose these patients for a phase 2 or 3 study to evaluate efficacy. To support this hypothesis, PF-06372865 shows a similar analgesic PainCart profile to pregabalin which did not demonstrate significant pain reduction in patient with neuropathic CLBP syndromes,[76] but it did yield positive outcomes in post-herpetic neuralgia patients,[80] giving more incentive to explore efficacy via this Alternative method.

Further investigation of PF-06372865 as an analgesic was discontinued, however, it is currently being studied for its antiepileptic properties.[81]

In **Chapter 3** two dose levels of PF-06273340 were under investigation, a peripherally restricted small molecule inhibitor of tropomyosin-related kinase (Trk) A, B and C. Nerve growth factor (NGF) is a key mediator of chronic pain that signals through, among others, TrkA, TrkB and TrkC. The 400 mg dose of PF-06273340 significantly reduced the hyperalgesia seen in the UVB heat model. The lower dose level of PF-06273340 did not show an effect on any of the endpoints, suggesting that the PainCart is able to detect active dose ranges of a compound. PF-06273340 showed a similar analgesic profile of PF-06273340 compared with ibuprofen, a non-steroidal anti-inflammatory drug (NSAIDs). The analgesic

effect of the high dose is in agreement with the expected mechanism of action of this molecule. NGF is upregulated in experimental models of inflammation, including UVB sensitization,[28,29] and anti-NGF monoclonal antibodies and Trk inhibitors (including PF-06273340) have shown efficacy in nonclinical models of inflammatory pain, *e.g.*, the UVB model. Because the NGF pathway involves NGF binding to the TrkA kinase receptor, inhibition of TrkA has been clinically validated as a target for pain. In situations such as prolonged inflammatory responses, analgesics that suppress NGF/TrkA signalling might be considered to be effective therapy. Moreover, anti-NGF or TrkA inhibitors, are also candidate analgesics in the treatment of chronic pain caused by osteoarthritis (OA). Clinical studies in patients with OA might therefore have been warranted, endorsed by the pain reducing properties of the NGF neutralizing antibody tanezumab in studies with these patient population.[38-41] Before PF-06273340 will move forward in studies with OA patients, it is essential to link it to a somatosensory phenotype within this patient population. It is well-known that the pathophysiology of OA pain is complex, with significant inter-individual variability in symptomatology. QST could be used to phenotype OA patients into sub-groups which might differ in treatment response. A recent study presented QST findings of patients with knee OA and demonstrated a reduced pain thresholds for mechanical hyperalgesia, cold pressor and CPM, and an amplified temporal summation compared with healthy volunteers. After treatment with a topical NSAIDs the CPM normalized while the other paradigm remained unchanged.[82] These findings cannot directly be correlated to the analgesic profile of PF-06273340. Further research is needed, for example to treat the same patient group with an anti-NGF compound. Unfortunately, the metabolism of PF-06273340 is mediated by aldehyde oxidase, leading to reduced confidence in the prediction of human metabolic clearance and to unpredictable toxicity and clinical safety. The latter is essential as pan-Trk inhibitors require restriction to the peripheral compartment to avoid undesirable side effects associated with Trk inhibition in the central nervous system (CNS).[42] Further development of PF-06273340 was discontinued.

Discussed in **Chapter 4** are the results of PF-05089771, a small molecule inhibitor of the voltage gated sodium channel 1.7 ($Na_V1.7$). A significant body of evidence implicates sodium channels in mediating the pathophysiological components of both neuropathic and nociceptive pain.[30-32] PF-05089771 was being developed for diabetic peripheral neuropathy alone and concomitantly administered with pregabalin. The aim was to assess the efficacy in the PainCart to evaluate for future potential additional pain indications for PF-05089771 in addition to diabetic peripheral neuropathy (DPN), and also provide clinical translation from these evoked pain endpoints in healthy subjects to the future outcome in a DPN Proof of Concept (POC) study to inform of the utility of the PainCart as a translatable clinical battery. PF-05089771, alone nor administered concomitantly with pregabalin, did not demonstrate an analgesic effect in any of the end points. The same lack of results were found in the POC study in DNP patients where a modest, but not statistically significant, pain relief was observed.[43] Possible reasons for the modest pain reduction that were opted are the dose selection, the inability to access the $Na_V1.7$ receptors in the CNS, the role of the peripheral nerve terminal in nociception generation, and whether selective $Na_V1.7$ blockage is sufficient.[43] An Alternative consideration is the influence that $Na_V1.7$ inhibitors have on the activation and inactivation of the $Na_V1.7$ receptor. BIIB074 is another $Na_V1.7$-selective, state-dependent, sodium channel blocker.[44] This compound causes an acceleration in the onset of inactivation of the $Na_V1.7$ receptor and a delayed recovery from the inactivation. Moreover, it does not affect the activation of the receptor.[45] BIIB074 is currently the only $Na_V1.7$ inhibitor that has moved forward into phase 3 clinical trials for continued investigation in patients with trigeminal neuralgia.

It can be hypothesized that the wrong patient population was selected for PF-05089771 where trigeminal neuralgia would have been a better fit. Trigeminal neuralgia is an idiopathic paroxysmal pain most often characterized by episodes of spontaneous, severe shooting or jabbing pain that may feel like an electric shock, in the area innervated by the trigeminal nerve, usually triggered by innocuous stimuli. $Na_V1.7$ is preferentially expressed in peripheral neurons, including trigeminal neurons, which supports further development of BIIB074, or PF-05089771 for that matter, in trigeminal neuralgia. BIIB074 has not been evaluated with the PainCart, but most likely would have affected the electrical and mechanical stimulation paradigms as these paradigms have the closest resemblance to the clinical symptoms. It is also expected to influence pain models that modulate sodium influx in the generation of action potentials. The capsaicin model is a hyperalgesia model by activation of the transient receptor potential vanilloid 1 receptor (TRPV1). Activation of TRPV1 produces a sodium influx that ultimately results in the release of a cocktail of neuropeptides initiating and modulating neurogenic inflammation.[83] It can be postulated that a $Na_V1.7$ inhibitor, such as PF-05089771 or BIIB074, may attenuate pain thresholds in a capsaicin model. Evaluation of the capsaicin-induced hyperalgesia model was described in **Chapter 8**.

In section two of this thesis the scientific results of several studies are presented regarding validation and improvement of pain models. In **Chapter 5**

we quantified the reproducibility of the pain models included in the PainCart. Reproducibility is a long-lasting and still ongoing debate in the scientific world. In scientific research, credibility is of utmost importance. Reproducibility of methods increases the power of a scientific claim. Unfortunately, irreproducibility of major findings in high-profile journals ranges from 75% to 90%.[33,34] Basically, there are two major camps: those who are for more reproducibility (Reproducibility movement) and those who are against. The Reproducibility movement states that it is, and has always been, an essential part of science; not doing so is simply bad science. It is an important step in the 'Scientific Method' allowing science to progress by building on previous work; without it progress slows. This requires the submission of the data and computational tools used to generate the results; without it results cannot be verified and built upon. Adherence to agreed guidelines for the conduct of experimental research is necessary, as well as access to the protocol and the collected data.[35] The opposing camps debates whether or not reproducibility, at least in the form proposed, is not now, nor has it ever been, has been an essential part of science.[36] The idea of a single well-defined scientific method resulting in an incremental, and cumulative, scientific process is, at the very best, moot.[36] Requiring the submission of data will encourage a level of distrust among researchers and promote the acceptance of papers based on narrow technical criteria.[36] Misconduct has always been part of science with surprisingly little consequence. The public's distrust is likely more to with the apparent variability of scientific conclusions.[36] Consensus on this topic seems unlikely. In our study we had full access to all collected data being that all four studies were conducted at the same centre (Centre for Human Drug Research (CHDR)), giving us the opportunity to evaluate the reproducibility of the pain models. We were able to replicate the results throughout all included studies to a reasonably expected degree (an inherent variability of biological systems taken into account), increasing the robustness and generalisability of the results. Reproducible results are important to obtain since these results are the foundation to initiate trustworthy advances in a research program.

In a double-blind, double-dummy, single dose, randomized, placebo-controlled, crossover study, described in **Chapter 6**, we explored the analgesic effects of a classical (paracetamol) and a non-classical (Δ9-Tetrahydrocannabino (Δ9-THC)) analgesic. To investigate the role of sedation rather than analgesic effects of psychoactive compounds, a negative control was included in this study in the form of the H1 antihistaminergic promethazine. The lack of effect of Δ9-THC in the PainCart confirms the suspicion on the value of cannabinoids in treating patients with chronic neuropathic pain. A recent systematic review concluded

that there is a lack of high-quality evidence for the efficacy of any cannabis-based medicine in any condition with chronic neuropathic pain.[46] At best, only few patients with neuropathic pain will benefit from long-term use of cannabis-based medicines.[46] The Special Interest Group on Neuropathic Pain (NeuPSIG) for the pharmacotherapy of neuropathic pain gave a weak recommendation against the use of cannabis-based medicines.[13] The use of cannabis as an analgesic should be evaluated at a regular base by the care-taker to avoid unnecessary exposure to harm in the absence of benefit. Adverse events, such as somnolence, sedation and feeling high may attribute to pain relief indirectly, but confusion and psychosis limit the clinical usefulness of cannabis-based medicines.[46]

The Bond and Lader set of visual analogue lines are used to quantify subjective effects of sedative agents. Δ-9-THC significantly reduced subjective alertness and significantly increased calmness compared with placebo, and promethazine significantly reduced subjective alertness compared with placebo. No analgesic effects were measured (for Δ9-THC and promethazine) by the PainCart, despite the presence of sedation as established with the Bond and Lader. The results described in **Chapter 6** may have been disappointing in terms of their analgesic profile, it proved an important quality that sedation is of no influence in the PainCart.

In **Chapter 7** we present the prevalence and characteristics of patients with postinflammatory hyperpigmentation (PIH) after ultraviolet-B (UVB) irradiation being used in the UVB inflammation model, and, based on these results, we improved the pain model to minimize the risk for development of this long-term side effect. Due to a relative short-term follow-up in previous conducted studies with the PainCart, we were unable to detect long-term adverse events as a result of the UVB irradiation. Under-reporting of adverse events may lead to a false sense of safety in a study design. Guidelines for detection and reporting of harm are needed, which would benefit most from a multidisciplinary approach.[47] Subjects should have an active role in reporting adverse events. A group of multidisciplinary investigators and patients have developed a patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE),[47] where subjects can report their adverse events after completion of the study. Additionally, investigators should report these adverse events in a standardized manner, journals should dedicate space for reports on harm, and regulatory agencies should oversee these reports.[48] Reporting of adverse events, even long-term adverse events, in clinical trials is essential to evaluate the subject's safety. It also gives the opportunity to learn from the incident and ultimately improve the design of the study in order to increase the subject's safety. Characteristics found

in the first study that were prone to the development of PIH, like UVB dosage and skin type, were adjusted in the second study. The aim was to create a pain model that is able to induce enough hyperalgesia to evaluate analgesic compounds without the high risk of developing long-lasting side effects. This study showed that irradiation with a two-fold, instead of a three-fold, of the minimal erythema dosage induced a long-lasting and stable hyperalgesia in subjects with the Fitzpatrick skin type of not higher than III. Whether or not this hyperalgesia is enough to evaluate efficacy of analgesic needs further investigation, for example, with ibuprofen, a non-steroidal anti-inflammatory drug (NSAIDs). This also gives an opportunity to compare the new results to results described in **Chapter 2-4**.

In the final chapter, **Chapter 8**, we aimed to validate – at CHDR - the capsaicin-induced hyperalgesia/allodynia model and to incorporate the pain model in the PainCart. Concerns about validity and the complexity of multimodal approach have existed for some time.[12] Validity and repeatability studies have been demonstrated for many pain models separately. Complexity of multimodal testing and their contributing factors, however, is little investigated. In the current study we were able to demonstrate that the test-rest variability was good. The study-to-study variation, in the current and four previous conducted PainCart studies without the capsaicin model, was small with consistent pain thresholds throughout all studies. The data suggest that, at least with these models, there is limited interference between the models which is essential in a multimodal model test setting. The capsaicin model is known to produce a primary mechanical allodynia/thermal hyperalgesia and a secondary mechanical allodynia.[49,50] In the current study no mechanical allodynia was induced, either on the primary or on the secondary area. A key learning from this validation study is a better understanding on the influence of the capsaicin formulation (*e.g.*, cream or ethanol solution) on mechanical stimulation. As described in this chapter, we believe that the formulation of the capsaicin might have negatively influenced the induction of secondary hyperalgesia. An Alternative consideration could be the study design where the timing and sequence of different activities and paradigms were the cause of a lack of positive results. Secondary hyperalgesia might be a short-lasting phenomenon which, in hindsight, should have been evaluated within 30-60 minutes after removal of the capsaicin cream. Further evaluation of all putative reasons should be done in order to optimize the capsaicin model to a pain model robust enough to explore analgesic profiles on candidate analgesic drugs.

FUTURE PERSPECTIVES

Despite the availability of strong analgesics, chronic pain is one of the largest unmet needs in medicine. Developing new and specific painkillers is even more important because many of the classic analgesics are highly addictive. Pain models help to predict the efficacy of a compound in the treatment of clinical pain, and may also predict in which types of pain the drug will be effective. However, development of new pain models and further refinement of existing pain models is needed.

One potential disadvantage of experimental pain models is that per definition, they only measure nociception, as affective components (fear, mood) and psychosocial factors that influence pain, are lacking. This may limit the extent to which pharmacological effects measured using pain models can be extrapolated to clinical pain. This will not, or to a lesser extent, be true for compounds that influence nociceptive processes, but will play an important role for new drugs that are expected to positively influence pain by (also) influencing affective components of pain. If a patient with moderate nociceptive pain also has a high level of anxiety, pain intensity will be importantly increased. New analgesic compounds are being developed that are expected to positively influence pain not only by decreasing pain directly, but also by decreasing the accompanying fear. At CHDR, we are currently developing a pain model in which we aim to lower pain thresholds by introducing fear of tissue damage using virtual reality (VR). The VRpain enhancement model may be able to include the affective component of pain to a (nociceptive) pain model.

It is known that non-nociceptive information regarding pain can both induce pain and modulate it,[51-53] suggesting that pain is evoked by information that must exceed a certain threshold, but not necessarily by a nociceptive stimulus. Acerra et al. demonstrated this in patients with complex regional pain syndrome (CRPS). These patients experienced pain when they were given the mere suggestion that they were touched, despite the lack of effective touch.[51] Virtual reality can be used as a supporting technique in pain relief.[54] Pain requires attention and VR may be particularly effective in distracting the patient's focus on pain during painful procedures. The virtual world generated by the computer can alleviate the pain in subjects submerged in VR. The stronger the illusion of the virtual world, the more VR will distract the patient, the more substantial the pain can be reduced.[55] Hoffman et al. showed that, compared with standard care (without VR), burn patients consistently reported a reduction in pain (> 30%) during wound care

and physical therapy.[54,56-58] SnowWorld has been designed specifically for this purpose (www.vrpain.com). We expect that this psychology can also be reversed. Additional attention to pain, together with the affective and psychosocial components (fear and anticipation), can be expected to increase the pain perception when a painful stimulus is administered. Exploring the role of VR in an experimental pain test setting may also teach us more about the role of how affective components influence pain.

Better understanding of existing pain models is an Alternative approach to increase the predictive value of analgesics. An established model to evaluate systemic inflammation is the human endotoxin model.[59] In this experimental setting, purified lipopolysaccharide (LPS) from E. coli or other Gram-negative bacteria is administered intravenously to healthy volunteers resulting in flu-like symptoms, increased production of C-reactive protein (CRP) and increased concentrations of pro- and anti-inflammatory cytokines. LPS from E. coli is predominantly used because of the high reproducibility of effects.[60-62] In various animal models and in clinical studies, the immune response induced by LPS has been demonstrated to modulate cognitive functions and nociceptive pain. LPS administration decreased pressure and heat pain thresholds, supporting a relationship between acute systemic inflammation and pain perception.[63,64] Combining the human endotoxin model with nociceptive testing could serve as a model for studying inflammatory hyperalgesia via mechanisms that are not yet covered by PainCart's UVB or capsaicin-induced heat pain model. Moreover, the model may be a good Alternative for the currently used UVB model, which produces a stable inflammatory-like hyperalgesia, but also unwanted long-lasting side effects (**Chapter 7**).

Central sensitization is an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. While neuropathic pain conditions are predominately the result of damage to the peripheral nervous system, their persistence appears to rely on maladaptive processes within the CNS,[49] making it an area of interest in human evoked pain model research. Central sensitization is also found in subjects with sleep disturbances.[65,66] Sleep deprivation affects the perception of pain (mainly thermal pain thresholds) as well as spontaneous pain.[67,68] Impaired sleep may affect processes relevant for the development and maintenance of chronic pain such as endogenous pain inhibition.[69] Multiple studies have reported that sleep-deprived subjects respond differently to evoked pain tests in a controlled setting. However it is still a topic of discussion as other clinical studies have provided conflicting results.[68,70-73] If validated, the sleep deprivation model may be used to demonstrate effects of relatively more centrally acting analgesic compounds. It may therefore serve as an Alternative to the capsaicin model (**Chapter 8**), where we were unable to demonstrate central sensitization using a mechanical stimulation paradigm.

The work presented in this thesis adds to the search of pain models with a high resemblance of clinical pain and gives incentive to investigate the translation of analgesic profiles deducted from multimodal pain model testing to somatosensory phenotyping by means of QST research. We evaluated existing pain models for their reliability and reproducibility in a multimodal model setting, we improved models which shifted to a negative risk-benefit assessment, and we incorporated a new pain model to the PainCart to increase its reach in the complex field of pain research.

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